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EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
04/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,962	BUNTINX, ERIK	
	Examiner	Art Unit	
	SARAH PIHONAK	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-109* is/are pending in the application.

4a) Of the above claim(s) *82-85,87-93,95-104,107 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,94,105,106 and 108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/2009,12/2/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/BE04/00172, filed on 12/2/04.

Priority

This application is a 371 (national stage application) of PCT/BE04/00172, filed on 12/4/04. The filing date of the instant application is 5/31/06. This application claims priority to the following foreign applications: 2451798, filed on 12/2/03; 03447279.5, filed on 12/2/03; 04447001.1, filed on 1/5/04; 04447066.4, filed on 3/18/04; 2461248, filed on 3/18/04; 04025035.9, filed on 10/21/04; 2004-349085, filed on 11/4/04; and 2487529, filed on 11/15/04. Certified copies of the foreign priority applications have been received. The instant application is also a continuation in part of the following applications: 10725965, filed on 12/2/03; 10/752423, filed on 1/6/04; and 10803793, filed on 3/18/04. Application No. 10/725965, 10/752423, and 10803793 provide support to the instant claims. Therefore, the priority and effective filing date given to the instant claims is that of the earliest filed application, 12/2/03.

Response to Remarks and Affadavit Submitted under Rule 132

1. The affadavit under 37 CFR 1.132 filed 12/30/2009 is insufficient to overcome the rejection of claims 86, 94, 105-106, and 108 based upon 35 USC § 103(a) as set forth in the last Office action because: the WO 01/41701 publication, Cremers et. al., teaches a composition comprised of an SSRI, such as escitolopram and a 5-HT_{2C} antagonist, partial agonist, or inverse agonist, with the dosage of the 5-HT_{2C} compound

ranging from 0.1 to 150 mg. daily. Van Oekelen et. al. teaches that pipamperone is a compound used therapeutically as a 5-HT_{2C} antagonist. Therefore, it would have been obvious to combine pipamperone within a dosage range of 0.1 to 150 mg. with escitalopram, because Cremers et. al. teaches that this dosage range of 5-HT_{2C} antagonist is effective when used in combination with an SSRI such as escitalopram. As such, it would have been prima facie obvious to administer a combination of escitalopram and pipamperone at a dosage of 5-15 mg. daily.

2. Applicant's remarks, regarding the rejection of claims 86, 94, 105-106, and 108 under 35 USC § 103(a) have been fully considered, but are not found persuasive. The Applicant has argued that pipamperone has a different binding affinity for the 5-HT_{2A} and 5-HT_{2C} receptors. At a lower dose of pipamperone, the 5-HT_{2A} and D_4 receptors are occupied by pipamperone, but not the 5-HT_{2C} and D_2 receptors. At the low dose of pipamperone (5-15 mg), the negative side effects due to binding of the drug to the D_2 receptors are avoided. Therefore, the Applicant has argued that due to the claimed low dose of pipamperone, the claims are novel and non-obvious over the prior art. The examiner disagrees. The WO 01/41701 publication, Cremers et. al., teaches the combination of an SSRI, such as escitalopram, and a compound having 5-HT_{2C} antagonistic, partial agonistic, or inverse agonistic activity. Cremers et. al. also teaches that the amount of the 5-HT_{2C} antagonist, partial agonist, or inverse agonist is between 0.1 to 150 mg. daily; van Oekelen et. al. teaches that pipamperone is a 5-HT antagonist with binding affinity for the 2C and 2A receptors. Therefore, as van Oekelen et. al.

teaches that pipamperone is a 5-HT_{2C} antagonist, it would have been prima facie obvious to combine pipamperone with escitalopram, as taught by Cremers et. al. The Applicant has argued that the low dose of pipamperone, between 5-15 mg., is not explicitly taught by the prior art, and that the art actually teaches away from this dosage range. The Applicant has also stated that the claimed dose of pipamperone is not from mere optimization, as the lower dosage of pipamperone is associated with fewer side effects, due to D_2 receptor related dopaminergic antagonism. Additionally, the Applicant has stated that the prior art teaches higher dosages of pipamperone, as evidenced by Squelart et. al., and Dipiperon. Applicant's remarks and discussion regarding the prosecution of co-pending applications 10/725965 and 10/752423, have been fully considered by the examiner. However, the claims are obvious over Cremers et. al., in view of van Oekelen et. al., because Cremers et. al. teaches that the dosage range for the 5-HT_{2C} antagonist is between 0.1 to 150 mg. daily. As the claimed dosage range of 5-15 mg. for pipamperone is within the dosage range of 5-HT_{2C} antagonist taught by Cremers et. al., it would have been obvious to administer the drug within this range. Therefore, the rejection of the claims under 35 USC § 103(a) was proper and is maintained, for reasons of record. For Applicant's convenience, this rejection will be restated below in the office action.

Applicant's remarks, regarding the rejection of claims 106 and 108 under 35 USC § 112, first paragraph, have been fully considered, but are not found persuasive. The claims have been amended to remove 'prodrugs', however, the Applicant maintains that it would have been routine for one of ordinary skill in the art to prepare active

metabolites of the claimed compounds. As discussed in the office action dated 6/2/2009, the prior art teaches that significant differences in potency and biological activity can exist between parent compounds and active metabolites. Therefore, it is unlikely that all metabolites of a given compound would have equivalent utility. The rejection under 35 USC § 112, first paragraph, is maintained, for reasons of record. For Applicant's convenience, this rejection will be reiterated below.

Applicant has not presented arguments or remarks regarding the rejection of claims 86, 94, and 105 for obviousness type double patenting over claim 41 of co-pending Application No. 10/725965. The claims of copending application No. 10/725965 are drawn to a pharmaceutical composition comprised of pipamperone in a dose of 5-15 mg., and a therapeutically effective amount of a selective serotonin re-uptake inhibitor; as the instant claims are also directed to this combination, the rejection for obviousness type double patenting is maintained. Accordingly, this action is made FINAL.

In the response filed on 12/2/2009, the Applicant has requested re-instatement and consideration of withdrawn species. The species election and restriction requirement are maintained by the examiner, for reasons of record. However, in the event that the independent claim and elected species are found free of the prior art, examination will be extended to other claimed species. Claims 82-85, 87-93, 95-104, 107, and 109 were previously withdrawn due to the restriction requirement.

3. Claims 86, 94, 105-106, and 108 were examined.

4. Claims 86, 94, 105-106, and 108 are rejected.

Claim Rejections-35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 86, 94, 105-106, and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cremers et. al., WO 01/41701 patent publication, in view of Van Oekelen et. al., *Eur. J. Pharm.*, **425**, pp. 21-32.

8. The WO '701 publication teaches a composition comprised of an SSRI and a compound having 5-HT_{2c} antagonistic, partial agonistic, or inverse agonistic activity (Abstract). Specifically, the WO '701 publication teaches that escitalopram can be selected as the SSRI (p. 6, line 29).

The WO '701 publication does not explicitly teach that the compound having 5-HT_{2c} antagonistic, partial agonistic, or inverse agonistic activity is pipamperone, or that the amount of pipamperone to be administered is a unitary dose between 5 and 20 mg.

9. Van Oekelen et. al. teaches that pipamperone is a 5-HT antagonist and has binding affinity for both the 5-HT_{2A} and 5-HT_{2c} receptors (p. 29, right column, top paragraph). Van Oekelen et. al. also teaches that pipamperone has been widely used for therapeutic use (p. 29, right column, top paragraph).

One of ordinary skill in the art would have been motivated to combine pipamperone with escitalopram, because pipamperone has been known in the art to be widely used in compositions for therapeutic purposes, and functions as a serotonin antagonist, with binding affinity for both the 5-HT_{2A} and 5-HT_{2C} receptors, as taught by Van Oekelen et. al. (p. 29, right column, top paragraph). The WO '701 publication teaches a composition comprised of both escitalopram, and an additional compound that functions as a 5-HT_{2C} antagonist, partial agonist, or inverse agonist. While the WO '701publication does not explicitly teach that pipamperone can be present in the composition, it is taught that the composition is comprised of a compound that functions as a 5-HT_{2C} antagonist, partial agonist, or inverse agonist (Abstract), and that this compound includes "antipsychotics having effect at 5-HT_{2C} receptors" (p. 12, lines 10-18). Van Oekelen et. al. proposes than pipamperone has an inverse agonistic effect on the 5-HT_{2C} receptor (p. 30, right column, last paragraph). Additionally, pipamperone has been commonly used for therapeutic purposes related to treatment of depression, anxiety, and other related disorders. As such, it would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to combine pipamperone with escitalopram, because the WO '701 publication teaches that escitalopram and an anti-depressant which has activity at the 5-HT_{2C} receptor are effective in compositions

for treating mood, depression and other anxiety disorders, and Van Oekelen teaches that pipamperone has binding affinity for the 5-HT_{2C} receptor.

It is noted that while the WO '701 publication does not explicitly state that the amount of pipamperone administered is a unitary dose between 5 to 20 mg., it is taught that the amount of 5-HT_{2C} antagonist, partial agonist, or inverse agonist to be administered ranges from 0.1 to 150 mg. daily (p. 14, lines 26-27). It would have been obvious to one of ordinary skill in the art that as pipamperone functions as an inverse agonist, the amount of pipamperone to be administered would also be within this range. The WO '701 publication also teaches unitary dosages (p. 15, lines 28-31).

Claim Rejections-35 USC § 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 106 and 108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating mood or anxiety disorders with a composition comprised of escitalopram and pipamperone, does not reasonably provide enablement for treating such disorders with all active metabolites of selective serotonin and nor-adrenaline reuptake inhibitors, hereafter referred to as SNRIs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See M.P.E.P. 2164.08. The reference of Meyer, *J. Pharmacokinetics and Biopharmaceutics*, **24**, pp. 449-459, is used in this rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a composition comprised of pipamperone and escitalopram, to be used for the treatment of mood or anxiety disorders. The claims also cite that the composition is comprised of active metabolites of SNRIs. Thus, the claims taken together with the specification imply all active metabolites of SNRIs can be used in a

composition for treating mood or anxiety disorders. However, the number of possible active metabolites of SNRIs can be considerably large, and not all of the active metabolites would be expected to have the same biological activity. Additionally, it is known in the art that some metabolites can be more toxic than the parent drug, which would make their administration undesirable.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The prior art teaches that pipamperone and escitalopram are both useful in compositions for treating mood and anxiety disorders. However, there is no such evidence in the prior art that all active metabolites of SNRIs would also be effective. The prior art does provide evidence that active metabolites of parent drugs can vary considerably, in terms of potency and toxicity, as taught by Meyer (p. 450, first paragraph). Furthermore, Meyer et. al. also teaches that drug metabolism is also genetically dependent, and that major differences can exist between different individuals' abilities to metabolize drugs (p. 453). Age, lifestyle, health, and other environmental factors can also have an effect on personal drug metabolism (p. 453). Therefore, it is unlikely that all active metabolites would have similar potency, and toxicological data as the parent compounds. Therefore, while studies are useful to determine which particular active metabolites would be expected to be beneficial, there exists unpredictability regarding whether all active metabolites of compounds would have similar benefits of the parent compounds.

(5) The relative skill of those in the art:

The relative skill of one in the art would be high, such as that of an MD.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for escitalopram and pipamperone for treating mood or anxiety disorders.

However, the specification does not provide guidance for all possible active metabolites of SNRIs to be administered as a composition for treating such disorders.

(8) The quantity of experimentation necessary:
Considering the state of the art as discussed by the references above, particularly with regards to the evidence of the prior art regarding active metabolites, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims. The prior art teaches that considerable differences can exist between active metabolites and parent compounds regarding activity, metabolism, and toxicity. Therefore, not all active metabolites of SNRIs would be expected to be as effective as the parent compounds. As such, one of ordinary skill in the art would be burdened with undue experimentation to determine specifically which active metabolites of prodrugs would be effective and safe for treating mood or anxiety disorders.

Claim Rejections-Obviousness Type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 86, 94, and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 41 of copending Application No. 10/725965. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both cite compositions comprised of pipamperone and a selective serotonin re-uptake inhibitor. The claims therefore overlap considerably in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 86, 94, and 105 are drawn to a composition comprised of pipamperone, in a unitary dosage between 5-15 mg., and a selective serotonin, nor-adrenaline and dopamine reuptake inhibitor. Claims 86, 94, and 105 also cite that the combination is

prepared as either for simultaneous, separate, or sequential administration. Claim 41 of the copending Application No. 10/725965 also cites a composition comprised of pipamperone in a dosage between 5-15 mg., and a selective serotonin reuptake inhibitor. While claims 41 of the copending application and claims 86, 94, and 105 of the instant application are not identical, the content of the claims is quite similar. Therefore claim 41 of the copending application and claims 86, 94, and 105 are obvious over each other.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information Disclosure Statement

15. The information disclosure statements (IDS) submitted on 5/18/2009 and 12/2/2009 were filed. The submission is in compliance with the provisions of 37

CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

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